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| EXAMINER | |
|---|---|
| GOON, SCARLETT Y | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

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| 11/12/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/734,573 | FRICK ET AL. | |
| | Examiner | Art Unit | |
| | SCARLETT GOON | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *29 July 2008 and 31 July 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 29 July 2008.

Claims 1-7 and 9-12 are currently pending in the instant application.

Claims 9-12 are withdrawn pursuant to a restriction requirement.

Claims 1-8 will be examined on its merits herein.

### *Priority*

This application claims priority to U.S. provisional application no. 60/466449 filed on 29 April 2003, German foreign application 10258008.1-43 filed on 12 December 2002, and PCT/EP03/13455 filed on 28 November 2003. A certified copy of foreign priority document 10258008.1-43 in German has been received. No English translation has been provided.

### *Information Disclosure Statement*

The information disclosure statements (IDS) dated 29 July 2008 and 31 July 2008 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

***Rejections Withdrawn***

In view of the cancellation of claim 8, all rejections made with respect to claim 8 in the previous Office Action are withdrawn.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some compounds of formula (I), does not reasonably provide enablement for all compounds of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a compound of formula (I) in which all variables are indicated within the claim.

Relative skill of those in the art: The relative skill of those in the art is high.

Breadth of claims: The claims are extremely broad in that they encompass a extremely large number of possible structural components for each variable of the compound of formula (I).

Amount of guidance/Existence of working examples: More importantly, there are working examples present for only a subset of the possible variations of compounds of formula (I). Working examples are only present for the compound of formula (I) wherein R1 and R2 are independently F or H, R3 is OH or F, R4 is OH, A is O, X is C, O, S or N, Y is N, O, or S, m is 2, R5 is H, OH, $CF_3$, $CH_3$, R6 is H or $CH_3$, B is $CH_2$ or $CONHCH_2$, n is 3, Cyc1 is a 6-membered saturated ring wherein one carbon atom may be replaced S, and R7, R8 and R9 are F, Cl, or $OCH_3$. No working examples are present for any other substituents of the variables claimed in instant claim 1, such as compounds wherein A is NH, $CH_2$ , S or a bond, m is 2, R5 is phenyl, benzyl, akenyl, or alkynl, R6 is cycloalkyl or phenyl, B is S or CHF, n is 1, 2 or, 4, and Cyc1 is a 3-, 4-, 5-, or 7-membered saturated, partially saturated or unsaturated ring.

Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

State of the prior art/Predictability or unpredictability of the art: The skilled artisan would view that the synthesis of all possible variations of the compounds of formula (I) would require much experimentation. For instance, reaction scheme A of the instant specification discloses the synthesis of compound 17 in Example 1 (p. 40). This scheme was subsequently used to synthesize other exemplary compounds as shown on p. 40-42 of the instant specification. However, because of the difference in electrophilic/nucleophilic characteristics between a N, O and C atom, and the different chemistries involved in the synthesis of O-glycoside, N-glycosides and C-glycosides, a skilled artisan would view that this scheme is not applicable to the of compounds wherein A is NH, $CH_2$ or a bond.

Kunz (PTO-892, Ref. V) teaches that for the construction of O-glycosidic linkages to serine or threonine derivatives, glycosyl halides and promotion by mercury or silver salts, in particular by silver triflate, is generally efficient (p. 268, first complete paragraph). Additionally, glycosyl trichloroacetimidates and thioglycosides are also useful donors in the synthesis of O-glycosides. The glycosyl halide method was described by Applicants in the synthesis of their O-glycosidic compounds. Kunz further indicates that contrary to O-glycosides, general access to N-glycopeptides is attained through glycosyl azides that are reduced to glycosylamines, which is then condensed with aspartic acid derivatives to give the N-glycoside (p. 268, first complete paragraph). It must be noted that although Kunz describes the synthesis with respect to glycopeptides, the same chemistry applies to structures wherein the aglycone is not a peptide or an amino acid. Therefore, one of ordinary skill in the art would immediately

be aware that in the synthesis of O-glycosides, the aglycone portion functions as the nucleophile whereas in the synthesis of N-glycosides, the anomeric atom of the sugar molecule must first be converted into an amine which then functions as the nucelophile. Thus, a skilled artisan would not be able to easily substitute a N atom in place of an O atom for variable A using the synthetic schemes and compounds disclosed in the instant application.

Giese *et al.* (PTO-892, Ref. W) teach that the synthesis of C-glycosides relies on the electrophilicity of the anomeric center and, therefore, involves the attack of an appropriate C-nucleophile (p. 507, paragraph 1). Several intermolecular methods and intramolecular methods are described on p. 510-517. As one can see from the carbon nucleophiles disclosed by Kunz, it is not readily apparent and accessible how the aglycones disclosed in the instant application can be used to synthesis C-glycosides. Furthermore, as the aglycone disclosed by Applicants is contained in an aromatic ring, the electronics of this structure would also pose an additional obstacle and thus require undue experimentation.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for making the claimed compounds as recited in the instant claims.

*Genetech*, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided and the lack of working examples, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,815,428 B2 to Ohsumi *et al.* (herein referred to as the '428 patent, of record), in view of journal publication by Díez-Sampedro *et al.* (PTO-892, Ref. U).

The Ohsumi '428 patent teaches pyrazole-O-glycoside derivatives represented by formulas (1A) and (1B) for use as a diabetic medicine (abstract; column 1, lines 55-67; column 2, lines 1-14; claim 1). Exemplary compounds 1-16 are also shown (columns 31-35). Pharmaceutical compositions comprising the aforementioned compounds inhibit the $Na^+$-dependent glucose transporter (SGLT), which reduces renal glucose reabsorption at renal uriniferous tubules (column 1, lines 15-18 and lines 37-40). As a result, the level of blood sugar decreases. SGLT-1 and SGLT-2 are known membrane proteins which transport glucose.

The Ohsumi '428 patent does not teach pyrazole-O-glycoside derivatives wherein the C-4 hydroxyl is substituted with a fluorine atom.

Díez-Sampedro *et al.* teach the effects of varying the hydroxyl groups on the glucose ring and its recognition by the $Na^+$-dependent glucose transporter (SGLT1). SGLT1 is highly selective for its natural substrates, D-glucose and D-galactose (abstract). Díez-Sampedro *et al.* individually substituted the different hydroxyl groups on the glucose ring with a hydrogen, fluorine or methyl group and studied the ability of SGLT1 in recognizing and binding the modified substrate (p. 49189, column 1, subsection "Compounds"; p. 49189, column 2, full paragraphs 3-5). The only increase in the apparent affinity, compared with glucose, was found when the equatorial hydroxyl group in the fourth position was replaced with a fluorine atom (4F4DOglc) where the $K_{0.5}$=0.07mM (p. 49189, column 2, fifth full paragraph). Since 4F4DOglc had a lower $K_{0.5}$ compared with glucose (six times higher affinity), Díez-Sampedro *et al.* concluded

that the hydrogen bond donation of the fourth position of glucose was detrimental to sugar binding (p. 49192, column 1, third full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Ohsumi '428 patent, regarding pyrazole-O-glycoside derivatives that inhibit the $Na^+$-dependent glucose transporter (SGLT) for use as a diabetic medicine, with the teachings of Díez-Sampedro *et al.*, regarding the increased apparent affinity of 4F4DOglc by SGLT as compared with the native glucose substrate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Díez-Sampedro *et al.*, that SGLT has a higher apparent affinity for the glucose substrate when the 4-hydroxyl group is replaced with a fluorine atom. A medicinal chemist would view that a compound with an increased apparent affinity for a receptor, as in the situation described by Díez-Sampedro *et al.*, can likely serve as an inhibitor of the substrate, and would thus have been motivated to synthesize such a compound as inhibitors of SGLT can be used as a diabetic medicine.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

*Response to Arguments*

Applicant's arguments with respect to claims 1-8 have been considered but are moot in view of the new ground(s) of rejection.

It is noted that Applicants' argue that Blanchard *et al.* disclose glycosylation/deglycosylation reactions on β-glycosidases, and not on SGLTs, which are

membrane transport proteins, as in the instant application. Applicants therefore argue that different enzymes have different recognition patterns for their target molecules. Blanchard *et al.* disclose/suggest fluorine substitution close to the anomeric center of the sugar in order to slow down or inhibit the activity of glycosidases whereas the instant application suggests substitution at the C-4 (or C-3) position. Applicants argue that although Goon *et al.* teach that substitution of a hydroxyl group with a fluorine atom might be tolerated by biosynthetic enzymes, the effects cannot be generalized, and therefore cannot be used in combination with Blanchard *et al.* and Ohsumi *et al.* to make a case for motivation to substitute a fluorine at the C-4 position. The teachings of Díez-Sampedro *et al.*, in the new ground of rejection above, disclose that modification of the C-4 hydroxyl group of glucose increases the apparent affinity of the 4F4DOglc by SGLT.

Thus, the claimed invention as a whole is *prima facie* obvious over U.S. Patent No. 6,815,428 B2 to Ohsumi *et al.*, in view of journal publication by Díez-Sampedro *et al.*

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this

application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer.
A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 15 copending Application No. 11/567,410.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the fluorine substituted compounds of claim 1 herein overlaps with compounds claim in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The rejection is still deemed proper and is therefore adhered to.

*Response to Arguments*

Applicants argue that since all other rejections of the instant application have been overcome, the double patenting rejection should be withdrawn. This argument is not persuasive in view of the new ground of rejection applied to claims 1-7 above, under 35 USC § 103.

The rejection is still deemed proper and is therefore adhered to.

***Conclusion***

No claims allowed. This rejection is made NON-FINAL due to the new/modified grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
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